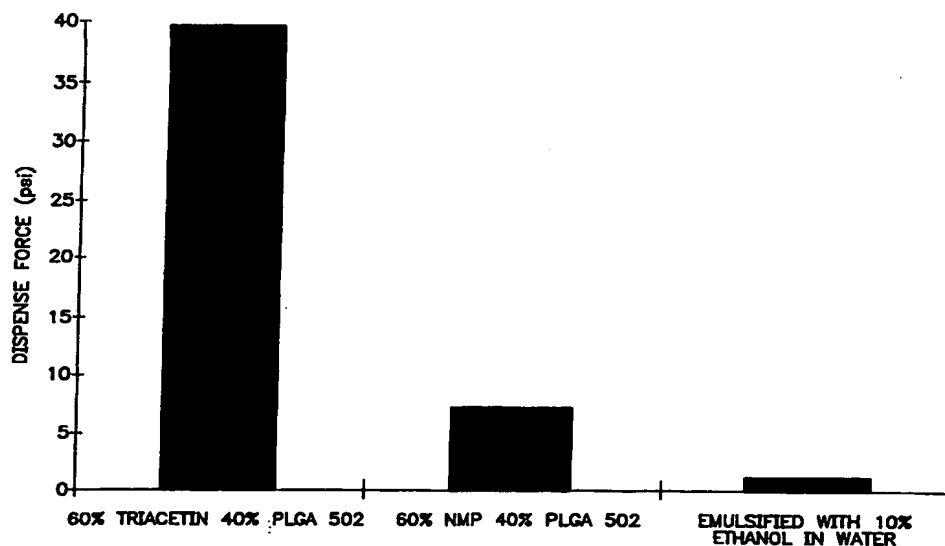




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/34		A2	(11) International Publication Number: WO 98/27962
			(43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23341		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 18 December 1997 (18.12.97)		Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US			
(71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US).			
(74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).			

(54) Title: INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF PREPARING THE COMPOSITION



(57) Abstract

An injectable depot gel composition containing a polymer, a solvent that can dissolve the polymer and thereby form a viscous gel, a beneficial agent; and an emulsifying agent in the form of a dispersed droplet phase in the viscous gel. The injectable depot gel composition can be prepared by mixing the polymer and the solvent so that the solvent dissolves the polymer and forms a viscous gel. The beneficial agent is dissolved or dispersed in the viscous gel and the emulsifying agent is mixed with the beneficial agent containing viscous gel. The emulsifying agent forms a dispersed droplet phase in the viscous gel to provide the injectable depot gel composition. The injectable depot gel composition can deliver a beneficial agent to a human or animal with a desired release profile.

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1 **INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF**
2 **PREPARING THE COMPOSITION**
3

4

5

6

7 **BACKGROUND OF THE INVENTION**

8

9 **Field of the Invention**

10

11 The present invention relates to a depot gel composition that can be injected
12 into a desired location and which can provide sustained release of a beneficial agent.

13 The present invention also relates to a method of preparing the composition.

14

15 **Description of the Related Art**

16

17 Biodegradable polymers have been used for many years in medical
18 applications. Illustrative devices composed of the biodegradable polymers include
19 sutures, surgical clips, staples, implants, and drug delivery systems. The majority
20 of these biodegradable polymers have been based upon glycoside, lactide,
21 caprolactone, and copolymers thereof.

22 The biodegradable polymers can be thermoplastic materials which means
23 that they can be heated and formed into various shapes such as fibers, clips, staples,
24 pins, films, etc. Alternatively, they can be thermosetting materials formed by
25 crosslinking reactions which lead to high-molecular-weight materials that do not
26 melt or form flowable liquids at high temperatures.

27 Although thermoplastic and thermosetting biodegradable polymers have
28 many useful biomedical applications, there are several important limitations to their
29 use in the bodies of various animals including humans, animals, birds, fish, and

1 reptiles. Because these polymers are solids, all instances involving their use have
2 required initially forming the polymeric structures outside the body, followed by
3 insertion of the solid structure into the body. For example, sutures, clips, and
4 staples are all formed from thermoplastic biodegradable polymers prior to use.
5 When inserted into the body, they retain their original shape. While this
6 characteristic is essential for some uses, it is a drawback where it is desired that the
7 material flow to fill voids or cavities where it may be most needed.

8 Drug delivery systems using thermoplastic or thermosetting biodegradable
9 polymers also have to be formed outside the body. In such instances, the drug is
10 incorporated into the polymer and the mixture is shaped into a certain form such a
11 cylinder, disc, or fiber for implantation. With such solid implants, the drug
12 delivery system has to be inserted into the body through an incision. These
13 incisions are sometimes larger than desired by the medical profession and
14 occasionally lead to a reluctance of the patients to accept such an implant or drug
15 delivery system. Nonetheless, both biodegradable and non-biodegradable
16 implantable drug delivery systems have been widely used successfully.

17 One reservoir device having a rate-controlling membrane and zero-order
18 release of an agent that is particularly designed for intraoral implantation is
19 described in U.S. Patent No. 5,085,866. The device is prepared from a core that is
20 sprayed with a solution having a polymer and a solvent that is composed of a
21 rapidly evaporating, low boiling point first solvent and a slowly evaporating, high
22 boiling second solvent.

23 Other illustrative osmotic delivery systems include those disclosed in U.S.
24 Patent Nos. 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318, 5,059,423,
25 5,112,614, 5,137,727, 5,151,093, 5,234,692, 5,234,693, 5,279,608, and
26 5,336,057. Pulsatile delivery devices are also known which deliver a beneficial
27 agent in a pulsatile manner as disclosed in U.S. Patent Nos. 5,209,746, 5,308,348,
28 and 5,456,679.

1 One way to avoid the incision needed to implant drug delivery systems is to
2 inject them as small particles, microspheres, or microcapsules. For example, U.S.
3 Patent No. 5,019,400 describes the preparation of controlled release microspheres
4 via a very low temperature casting process. These materials may or may not
5 contain a drug which can be released into the body. Although these materials can
6 be injected into the body with a syringe, they do not always satisfy the demand for a
7 biodegradable implant. Because they are particulate in nature, they do not form a
8 continuous film or solid implant with the structural integrity needed for certain
9 prostheses. When inserted into certain body cavities such as a mouth, a periodontal
10 pocket, the eye, or the vagina where there is considerable fluid flow, these small
11 particles, microspheres, or microcapsules are poorly retained because of their small
12 size and discontinuous nature. Further, the particles tend to aggregate and thus their
13 behavior is hard to predict. In addition, microspheres or microcapsules prepared
14 from these polymers and containing drugs for release into the body are sometimes
15 difficult to produce on a large scale, and their storage and injection characteristics
16 present problems. Furthermore, one other major limitation of the microcapsule or
17 small-particle system is their lack of reversibility without extensive surgical
18 intervention. That is, if there are complications after they have been injected, it is
19 considerably more difficult to remove them from the body than with solid implants.
20 A still further limitation on microparticles or microcapsulation is the difficulty in
21 encapsulating protein and DNA-based drugs without degradation caused by solvents
22 and temperature extremes.

23 The art has developed various drug delivery systems in response to the
24 aforementioned challenges. For instance, U.S. Patent No. 4,938,763 and its
25 divisional U.S. Patent No. 5,278,201 relate to a biodegradable polymer for use in
26 providing syringeable, in-situ forming, solid biodegradable implants for animals. In
27 one embodiment, a thermoplastic system is used wherein a non-reactive polymer is
28 dissolved in a biocompatible solvent to form a liquid which is placed in the animal
29 wherein the solvent dissipates to produce the solid implant. Alternatively, a

1 thermosetting system is used wherein effective amounts of a liquid acrylic ester-
2 terminated, biodegradable prepolymer and a curing agent are formed and the liquid
3 mixture is placed within the animal wherein the prepolymer cures to form the solid
4 implant. It is stated that the systems provide a syringeable, solid biodegradable
5 delivery system by the addition of an effective level of a biologically active agent to
6 the liquid before the injection into the animal.

7 U.S. Patent No. 5,242,910 describes a sustained release composition for
8 treating periodontal disease. The composition comprises copolymers of lactide and
9 glycolide, triacetin (as a solvent/plasticizer) and an agent providing relief of oral
10 cavity diseases. The composition can take the form of a gel and can be inserted into
11 a periodontal cavity via a syringe using either a needle or a catheter. As additional
12 optional components, the composition can contain surfactants, flavoring agents,
13 viscosity controlling agents, complexing agents, antioxidants, other polymers,
14 gums, waxes/oils, and coloring agents. One illustrative viscosity controlling agent
15 set forth in one of the examples is polyethylene glycol 400.

16 With solvent-based depot compositions comprised of a polymer dissolved in
17 a solvent, one problem which exists is that the composition solidifies slowly after
18 injection as solvent diffuses from the depot. Since these compositions need to be
19 non-viscous in order to be injected, a large percentage of drug is released as the
20 system forms by diffusion of the solvent. This effect is referred to as a "burst"
21 effect. In this respect, it is typical for solvent-based compositions to have a drug
22 burst wherein 30-75% of the drug contained in the composition is released within
23 one day of the initial injection.

24

1 In yet another aspect, the invention provides an injectable depot gel
2 composition comprising:

3 A) a biocompatible polymer;

4 B) a solvent that dissolves the polymer and forms a viscous gel; and

5 C) an emulsifying agent in the form of a dispersed droplet phase in the
6 viscous gel.

7 In an additional aspect, the invention provides a kit adapted to provide an
8 injectable depot composition comprising as kit components: (a) a biocompatible
9 polymer and a solvent that dissolves the polymer and forms a viscous gel; (b)
10 emulsifying agent; and (c) beneficial agent.

11

12 BRIEF DESCRIPTION OF THE DRAWINGS

13

14 The foregoing and other objects, features and advantages of the present
15 invention will be more readily understood upon reading the following detailed
16 description in conjunction with the drawings in which:

17 Figure 1 is a graph illustrating the dispense force required to dispense the
18 emulsified and non-emulsified viscous gel compositions through a 20 gauge needle
19 in psig at 2 cc/min;

20 Figure 2 is a graph illustrating the release profiles of lysozyme from three
21 different compositions in days; and

22 Figure 3 is a graph illustrating the viscosity profiles at different shear rates
23 of water alone and of an aqueous mixture of ethanol, and of the viscous gel without
24 emulsifying agent.

25

1 DESCRIPTION OF THE PREFERRED EMBODIMENTS

2

3 As explained above, one aspect of the present invention relates to an
4 injectable depot gel composition comprising:

5 A) a biocompatible polymer;

6 B) a solvent that dissolves the biocompatible polymer and forms a viscous
7 gel;

8 C) a beneficial agent; and

9 D) an emulsifying agent in the form of a dispersed droplet phase in the
10 viscous gel.

11 The polymer, solvent and emulsifying agents of the invention must be
12 biocompatible, that is they must not cause irritation or necrosis in the environment
13 of use. The environment of use is a fluid environment and may comprise a
14 subcutaneous or intramuscular portion or body cavity of a human or animal.

15 Polymers that may be useful in the invention may be biodegradable and may
16 include, but are not limited to polylactides, polyglycolides, polycaprolactones,
17 polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters,
18 polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates,
19 polyphosphazenes, succinates, poly(malic acid), poly(amino acids),
20 polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan,
21 and copolymers, terpolymers and mixtures thereof.

22 The polymer may be a polylactide, that is, a lactic acid-based polymer that
23 can be based solely on lactic acid or can be a copolymer based on lactic acid and
24 glycolic acid which may include small amounts of other comonomers that do not
25 substantially affect the advantageous results which can be achieved in accordance
26 with the present invention. As used herein, the term "lactic acid" includes the
27 isomers L-lactic acid, D-lactic acid, DL-lactic acid and lactide while the term
28 "glycolic acid" includes glycolide. The polymer may have a monomer ratio of
29 lactic acid/glycolic acid of from about 100:0 to about 15:85, preferably from about

1 60:40 to about 75:25 and an especially useful copolymer has a monomer ratio of
2 lactic acid/glycolic acid of about 50:50.

3 The lactic acid-based polymer has a number average molecular weight of
4 from about 1,000 to about 120,000, preferably from about 10,000 to about 30,000
5 as determined by gas phase chromatography. As indicated in aforementioned U.S.
6 Patent No. 5,242,910, the polymer can be prepared in accordance with the
7 teachings of U.S. Patent No. 4,443,340. Alternatively, the lactic acid-based
8 polymer can be prepared directly from lactic acid or a mixture of lactic acid and
9 glycolic acid (with or without a further comonomer) in accordance with the
10 techniques set forth in U.S. Patent No. 5,310,865. The contents of all of these
11 patents are incorporated by reference. Suitable lactic acid-based polymers are
12 available commercially. For instance, 50:50 lactic acid:glycolic acid copolymers
13 having molecular weights of 10,000, 30,000 and 100,000 are available from
14 Boehringer Ingelheim (Petersburg, VA).

15 The biocompatible polymer is present in the composition in an amount
16 ranging from about 5 to about 80% by weight, preferably from about 20 to about
17 50% by weight and often 35 to 45% by weight of the viscous gel, the viscous gel
18 comprising the combined amounts of the biocompatible polymer and the solvent.
19 Once in place in the environment of use, the solvent will diffuse slowly away from
20 the depot and the polymer will slowly degrade by hydrolysis.

21 The solvent must be biocompatible and is selected so as to dissolve the
22 polymer to form a viscous gel that can maintain particles of the beneficial agent
23 dissolved or dispersed and isolated from the environment of use prior to release.
24 Illustrative solvents which can be used in the present invention include but are not
25 limited to triacetin, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl
26 acetate, benzyl benzoate, ethyl acetate, methyl ethyl ketone, dimethylformamide,
27 dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid,
28 and 1-dodecylazacyclo-heptan-2-one and mixtures thereof. The preferred solvents
29 are triacetin and N-methyl-2-pyrrolidone. Triacetin provides a high level of

1 polymer dissolution which leads to greater gel viscosities, with attendant higher
2 force needed to dispense the viscous gel when compared with other solvents. These
3 characteristics enable the beneficial agent to be maintained without exhibiting a
4 burst effect, but make it difficult to dispense the gel through a needle. For instance,
5 as shown in Figure 1, a gel prepared from 40% by weight of a 50:50 lactic
6 acid:glycolic polymer and 60% by weight of triacetin required about 40 psig to
7 dispense the gel through a standard 20 gauge needle at 2 cc/min while a gel
8 prepared from the same amount of polymer with 60% by weight of N-methyl-2-
9 pyrrolidone required only about 8 psig. Figure 1 further shows that when the
10 emulsifying agent (in this case 33% by weight of a 10% ethanol solution) is added
11 to the viscous gel according to the invention, the dispense force needed is only
12 about 2 psig. The shear thinning characteristics of the depot gel compositions of the
13 present invention allow them be readily injected into an animal including humans
14 using standard gauge needles without requiring undue dispensing pressure.

15 The solvent is typically present in an amount of from about 95 to about 20%
16 by weight and is preferably present in an amount of from about 80 to about 50% by
17 weight and often 65 to 55% by weight of the viscous gel, that is the combined
18 amounts of the polymer and the solvent. The viscous gel formed by mixing the
19 polymer and the solvent typically exhibits a viscosity of from about 1,000 to about
20 200,000 poise, preferably from about 5 to about 50,000 poise measured at a 1.0 sec⁻¹
21 shear rate and 25° C using a Haake Viscometer at about 1-2 days after mixing is
22 completed. Mixing the polymer with the solvent can be achieved with conventional
23 low shear equipment such as a Ross double planetary mixer for from about 1 to
24 about 2 hours.

25 The beneficial agent can be any physiologically or pharmacologically active
26 substance or substances optionally in combination with pharmaceutically acceptable
27 carriers and additional ingredients such as antioxidants, stabilizing agents,
28 permeation enhancers, etc. that do not substantially adversely affect the
29 advantageous results that can be attained by the present invention. The beneficial

1 agent may be any of the agents which are known to be delivered to the body of a
2 human or an animal and that are preferentially soluble in water rather than in the
3 polymer-dissolving solvent. These agents include drug agents, medicaments,
4 vitamins, nutrients, or the like. Included among the types of agents which meet this
5 description are nutrients, vitamins, food supplements, sex sterilants, fertility
6 inhibitors and fertility promoters.

7 Drug agents which may be delivered by the present invention include drugs
8 which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the
9 skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory
10 system, synaptic sites, neuroeffector junctional sites, endocrine and hormone
11 systems, the immunological system, the reproductive system, the skeletal system,
12 autacoid systems, the alimentary and excretory systems, the histamine system and
13 the central nervous system. Suitable agents may be selected from, for example,
14 proteins, enzymes, hormones, polynucleotides, nucleoproteins, polysaccharides,
15 glycoproteins, lipoproteins, polypeptides, steroids, analgesics, local anesthetics,
16 antibiotic agents, anti-inflammatory corticosteroids, ocular drugs and synthetic
17 analogs of these species.

18 Examples of drugs which may be delivered by the composition of the present
19 invention include, but are not limited to prochlorperazine edisylate, ferrous sulfate,
20 aminocaproic acid, mecamylamine hydrochloride, procainamide hydrochloride,
21 amphetamine sulfate, methamphetamine hydrochloride, benzamphetamine
22 hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol
23 chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate,
24 scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin
25 hydrochloride, methylphenidate hydrochloride, theophylline choline, cephalixin
26 hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate,
27 phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythryl
28 tetranitrate, digoxin, isofluorophate, acetazolamide, methazolamide,
29 bendroflumethiazide, chloropromazine, tolazamide, chlormadinone acetate,

1 phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole,
2 erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate,
3 dexamethasone and its derivatives such as betamethasone, triamcinolone,
4 methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl
5 ether, prednisolone, 17 α -hydroxyprogesterone acetate, 19-nor-progesterone,
6 norgestrel, norethindrone, norethisterone, norethiederone, progesterone,
7 norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen,
8 sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol,
9 atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine,
10 methyl dopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen,
11 ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate,
12 vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz,
13 hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin,
14 alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine,
15 nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine,
16 lisinolpril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine,
17 sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam,
18 amitriptyline, and imipramine. Further examples are proteins and peptides which
19 include, but are not limited to, bone morphogenic proteins, insulin, colchicine,
20 glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones,
21 calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating
22 hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine
23 somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, somatostatin,
24 lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and
25 antagonists, leuprolide, interferons, interleukins, growth hormones such as human
26 growth hormone, bovine growth hormone and porcine growth hormone, fertility
27 inhibitors such as the prostaglandins, fertility promoters, growth factors, coagulation
28 factors, human pancreas hormone releasing factor, analogs and derivatives of these

1 compounds, and pharmaceutically acceptable salts of these compounds, or their
2 analogs or derivatives.

3 To the extent not mentioned in the previous paragraph, the beneficial agents
4 described in aforementioned U.S. Patent No. 5,242,910 can also be used. One
5 particular advantage of the present invention is that materials, such as proteins, as
6 exemplified by the enzyme lysozyme, and cDNA, and DNA incorporated into
7 vectors both viral and nonviral, which are difficult to microcapsulate or process into
8 microspheres can be incorporated into the compositions of the present invention
9 without the level of degradation experienced with other techniques.

10 The beneficial agent is preferably incorporated into the viscous gel formed
11 from the polymer and the solvent in the form of particles typically having an
12 average particle size of from about 0.1 to about 100 microns, preferably from about
13 1 to about 25 microns and often from 2 to 10 microns. For instance, particles
14 having an average particle size of about 5 microns have been produced by spray
15 drying or spray freezing an aqueous mixture containing 50% sucrose and 50%
16 chicken lysozyme (on a dry weight basis). Such particles have been used in certain
17 of the examples illustrated in the figures.

18 To form a suspension of particles of the beneficial agent in the viscous gel
19 formed from the polymer and the solvent, any conventional low shear device can be
20 used such as a Ross double planetary mixer at ambient conditions. In this manner,
21 efficient distribution of the beneficial agent can be achieved substantially without
22 degrading the beneficial agent.

23 The beneficial agent is typically dissolved or dispersed in the composition in
24 an amount of from about 1 to about 50% by weight, preferably in an amount of
25 from about 5 to about 25% and often 10 to 20% by weight of the combined amounts
26 of the polymer, solvent and beneficial agent. Depending on the amount of
27 beneficial agent present in the composition, one can obtain different release profiles.
28 More specifically, for a given polymer and solvent, by adjusting the amounts of
29 these components and the amount of the beneficial agent, one can obtain a release

1 profile that depends more on the degradation of the polymer than the diffusion of
2 the beneficial agent from the composition or vice versa. In this respect, at lower
3 beneficial agent loading rates, one generally obtains a release profile reflecting
4 degradation of the polymer wherein the release rate increases with time. At higher
5 loading rates, one generally obtains a release profile caused by diffusion of the
6 beneficial agent wherein the release rate decreases with time. At intermediate
7 loading rates, one obtains combined release profiles so that if desired, a
8 substantially constant release rate can be attained. While the particular release rate
9 depends on the particular circumstances, such as the beneficial agent to be
10 administered, release rates on the order of from about 1 to about 10 micrograms/day
11 for periods of from about 7 to about 90 days can be obtained. Further, the dose of
12 beneficial agent may be adjusted by adjusting the amount of injectable depot gel
13 injected. As will be apparent from the following results, one can avoid a burst
14 effect and administer on the order of 1% by weight of the beneficial agent in the
15 composition during the first day.

16 Figure 2 shows the release rates obtained from the compositions described
17 with regard to Figure 1. The gel prepared from 40% by weight of a 50:50 lactic
18 acid:glycolic polymer and 60% by weight triacetin is thick and thus difficult to
19 inject but shows little burst (less than 2% of the beneficial agent is delivered in the
20 first eight days). The gel prepared from 40% by weight of a 50:50 lactic
21 acid:glycolic polymer and 60% by weight N-methyl-2-pyrrolidone is thin and
22 injectable but shows a large burst (greater than 70% of the beneficial agent is
23 delivered in the first eight days). The gel prepared from 27% by weight of a 50:50
24 lactic acid:glycolic polymer, 40% by weight triacetin and 33% by weight of a 10%
25 ethanol, 90% isotonic saline solution is thin and injectable and shows little burst
26 (less than 10% of the beneficial agent is delivered in the first eight days). In each
27 case, lysozyme is the beneficial agent and comprises 20% by weight of the
28 combined beneficial agent, polymer and solvent formulation.

1 The emulsifying agent constitutes an important aspect of the present
2 invention. When the emulsifying agent is mixed with the viscous gel formed from
3 the polymer and the solvent using conventional static or mechanical mixing devices,
4 such as an orifice mixer, the emulsifying agent forms a separate phase composed of
5 dispersed droplets of microscopic size that typically have an average diameter of
6 less than about 100 microns. The continuous phase is formed of the polymer and
7 the solvent. The particles of the beneficial agent may be dissolved or dispersed in
8 either the continuous phase or the droplet phase. In the resulting thixotropic
9 composition, the droplets of emulsifying agent elongate in the direction of shear and
10 substantially decrease the viscosity of the viscous gel formed from the polymer and
11 the solvent. For instance, with a viscous gel having a viscosity of from about 5,000
12 to about 50,000 poise measured at 1.0 sec^{-1} at 25°C , one can obtain a reduction in
13 viscosity to less than 100 poise when emulsified with a 10% ethanol/water solution
14 at 25°C as determined by Haake rheometer. Because dispersion and dissolution of
15 the particles of beneficial agent in the emulsifying agent proceeds more rapidly than
16 does dissolution or dispersion of the beneficial agent in the viscous polymer, the
17 beneficial agent can be mixed with the emulsifying agent just prior to the time of
18 use. This permits the beneficial agent to be maintained in a dry state prior to use,
19 which may be advantageous in those instances where long term stability of the
20 beneficial agent in the viscous gel is of concern. Additionally, since the beneficial
21 agent will remain in the droplet phase that is entrapped within the viscous gel as it
22 forms, it is possible to select an emulsifying agent in which the drug is optimally
23 stable and thus prolong stability of the beneficial agent in the gel composition. An
24 added benefit is the opportunity to program the release of beneficial agent via
25 diffusion through the porous structure of the implant, rather than by degradation and
26 dissolution of the polymer structure.

27 When dissolution or dispersion of the beneficial agent in the emulsifying
28 agent is intended, the injectable depot of this invention may be provided as a kit,
29 having kit components comprising (a) a mixture of polymer and solvent, (b)

1 emulsifying agent and (c) beneficial agent. Prior to use the beneficial agent is mixed
2 with the emulsifying agent, and that solution or suspension is mixed with the
3 polymer/solvent mixture to prepare the injectable depot implant for use.

4 The emulsifying agent is present in an amount ranging from about 5 to about
5 80%, preferably from about 20 to about 60% and often 30 to 50% by weight based
6 on the amount of the injectable depot gel composition, that is the combined amounts
7 of polymer, solvent, emulsifying agent and beneficial agent. Illustrative

8 emulsifying agents are water, alcohols, polyols, esters, carboxylic acids, ketones,
9 aldehydes and mixtures thereof. Preferred emulsifying agents are alcohols,
10 propylene glycol, ethylene glycol, glycerol, water, and solutions and mixtures
11 thereof. Especially preferred are water, ethanol, and isopropyl alcohol and
12 solutions and mixtures thereof. The type of emulsifying agent affects the size of the
13 dispersed droplets. For instance, ethanol will provide droplets that have average
14 diameters that can be on the order of ten times larger than the droplets obtained with
15 an isotonic saline solution containing 0.9% by weight of sodium chloride at 21°C.

16 While normally no other components are present in the composition, to the
17 extent that conventional optional ingredients are desired, such as polyethylene
18 glycol, hygroscopic agents, stabilizing agents and others, they are used in an
19 amount that does not substantially affect the advantageous results which can be
20 attained in accordance with the present invention.

21 To illustrate various aspects of the invention further, Figure 3 shows the
22 viscosities at different shear rates using water alone and an aqueous mixture
23 containing 10% by volume of ethanol at a weight ratio of 2:1 (gel:emulsifying
24 agent) using a viscous gel formed from 50% by weight of a 50:50 lactic
25 acid:glycolic acid copolymer and 50% by weight of triacetin compared to the
26 viscosities of the viscous gel without emulsifying agent.

27 It is to be understood that the emulsifying agent of the present invention does
28 not constitute a mere diluent that reduces viscosity by simply decreasing the
29 concentration of the components of the composition. The use of conventional

1 diluents can reduce viscosity, but can also cause the burst effect mentioned
2 previously when the diluted composition is injected. In contrast, the injectable
3 depot composition of the present invention can be formulated to avoid the burst
4 effect by selecting the emulsifying agent so that once injected into place, the
5 emulsifying agent has little impact on the release properties of the original system.
6 Further compositions without beneficial agent may be useful for wound healing,
7 bone repair and other structural support purposes.

8 To further understand the various aspects of the present invention, the results
9 set forth in the previously described Figures were obtained in accordance with the
10 following examples.

11

12 Example 1

13 Lysozyme particles were made by spray drying 50% sucrose and 50%
14 chicken lysozyme (on a dry weight basis).

15 A viscous gel material was prepared by heating 60% by weight of triacetin
16 with 40% by weight of a 50:50 lactic acid:glycolic acid copolymer to 37°C
17 overnight. The viscous gel was allowed to cool to room temperature while mixing
18 continued. The lysozyme particles were added to the viscous gel in a ratio of 20:80
19 lysozyme particles:gel (by weight). The combination was mixed for 5 minutes.
20 Immediately prior to use, a 10% ethanol, 90% isotonic saline solution was added as
21 the emulsifying agent. The emulsifying agent comprised 1/3 of the total injectable
22 depot gel composition. 0.5 grams of this injectable depot composition was then
23 injected into a rat.

24

Example 2

25 A viscous gel material is prepared by heating 60% by weight of triacetin
26 with 40% by weight of a 50:50 lactic acid:glycolic acid copolymer to 37°C
27 overnight. The viscous gel is allowed to cool to room temperature while mixing is
28 continued. Immediately prior to use, lysozyme particles, prepared as in Example 1
29 and in the same amount, are combined with a 10% ethanol, 90% isotonic saline

1 solution, as an emulsifying agent, in the amount used in Example 1. The
2 emulsifying agent-lysozyme solution is mixed with the amount of gel material used
3 in Example 1 to form an injectable depot gel composition. The fabricated injectable
4 depot gel composition is suitable for injection into an animal.

5 In accordance with various aspects of the present invention, one or more
6 significant advantages can be obtained. More specifically, using simple processing
7 steps, one can obtain a depot gel composition that can be injected into place in an
8 animal without surgery using a low dispensing force through standard needles.
9 Once in place, the composition will quickly return to its original viscosity and may
10 exhibit rapid hardening so as to substantially avoid a burst effect and provide the
11 desired beneficial agent release profile. Furthermore, once the beneficial agent has
12 been fully administered, there is no need to remove the composition since it is fully
13 biodegradable. As a still further advantage, the present invention avoids the use of
14 microparticle or microcapsulation techniques which can degrade certain beneficial
15 agents, like peptide and nucleic acid-based drugs and which microparticles and
16 microcapsules maybe difficult to remove from the environment of use. Since the
17 viscous gel is formed without the need for water, temperature extremes, or other
18 solvents, suspended particles of beneficial agent remain dry and in their original
19 configuration, which contributes to the stability of thereof. Further, since a mass is
20 formed, the injectable depot gel composition may be retrieved from the environment
21 of use if desired.

22 The above-described exemplary embodiments are intended to be illustrative
23 in all respects, rather than restrictive, of the present invention. Thus the present
24 invention is capable of many variations in detailed implementation that can be
25 derived from the description contained herein by a person skilled in the art. All
26 such variations and modifications are considered to be within the scope and spirit of
27 the present invention as defined by the following claims.

1 WE CLAIM:

2 1. An injectable depot gel composition comprising:

3 A) a biocompatible polymer;

4 B) a solvent that dissolves the biocompatible polymer and forms a viscous
5 gel;

6 C) a beneficial agent; and

7 D) an emulsifying agent in the form of a dispersed droplet phase in the
8 viscous gel.

9

10 2. The injectable gel depot composition of claim 1 wherein the

11 biocompatible polymer is selected from the group consisting of polylactides,

12 polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes,

13 polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals,

14 polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly(malic

15 acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,

16 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and mixtures

17 thereof.

18

19 3. The injectable depot gel composition of claim 1 wherein the

20 biocompatible polymer is a lactic acid-based polymer.

21

1 4. The injectable depot gel composition of claim 3 wherein the lactic acid-
2 based polymer has a monomer ratio of lactic acid to glycolic acid in the range of
3 100:0 to about 15:85.

4

5 5. The injectable depot gel composition of claim 3 wherein the lactic acid-
6 based polymer has a number average molecular weight of from 1,000 to 120,000.

7

8 6. The injectable depot gel composition of claim 1 wherein the solvent that
9 can dissolve the biocompatible polymer to form a viscous gel is selected from the
10 group consisting of triacetin, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol
11 formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide,
12 dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid,
13 and 1-dodecylazacyclo-heptan-2-one and mixtures thereof.

14

15 7. The injectable depot gel composition of claim 1 wherein the solvent is
16 selected from the group consisting of triacetin and N-methyl-2-pyrrolidone, and
17 mixtures thereof.

18

19 8. The injectable depot gel composition of claim 1 wherein the solvent is
20 triacetin.

21

1 9. The injectable depot gel composition of claim 1 wherein the polymer is
2 present in an amount of from 5 to 80% by weight of the combined amounts of the
3 polymer and the solvent.

4
5 10. The injectable depot gel composition of claim 1 wherein the solvent is
6 present in an amount of from 95 to 20% by weight of the combined amounts of the
7 polymer and the solvent.

8
9 11. The injectable depot gel composition of claim 1 wherein the viscous gel
10 formed by the polymer and the solvent has a viscosity of from 1,000 to 200,000
11 poise.

12
13 12. The injectable depot gel composition of claim 1 wherein the beneficial
14 agent is a drug.

15
16 13. The injectable depot gel composition of claim 1 wherein the beneficial
17 agent is a peptide.

18
19 14. The injectable depot gel composition of claim 1 wherein the beneficial
20 agent is a protein.

21
22 15. The injectable depot gel composition of claim 1 wherein the beneficial
23 agent is growth hormone.

1
2 16. The injectable depot gel composition of claim 1 wherein the beneficial
3 agent is present in an amount of from 1 to 50% by weight of the combined amounts
4 of the polymer, the solvent and the beneficial agent.

5
6 17. The injectable depot gel composition of claim 1 wherein the beneficial
7 agent is in the form of particles dispersed or dissolved in the viscous gel.

8
9 18. The injectable depot gel composition of claim 17 wherein the beneficial
10 agent is in the form of particles having an average particle size of from 0.1 to 100
11 microns.

12
13 19. The injectable depot gel composition of claim 1 wherein the emulsifying
14 agent is selected from the group consisting of water, alcohols, polyols, esters,
15 carboxylic acids, ketones, aldehydes and mixtures thereof.

16
17 20. The injectable depot gel composition of claim 1 wherein the emulsifying
18 agent is selected from the group consisting of alcohols, propylene glycol, ethylene
19 glycol, glycerol, water and solutions and mixtures thereof.

20
21 21. The injectable depot gel composition of claim 1 wherein the emulsifying
22 agent is selected from the group consisting of ethanol, isopropyl alcohol, water,
23 solutions thereof, and mixtures thereof.

24

1 22. The injectable depot gel composition of claim 1 wherein the emulsifying
2 agent is water.

3
4 23. The injectable depot gel composition of claim 1 wherein the emulsifying
5 agent is present in an amount of from 5 to 80% by weight of the injectable depot gel
6 composition.

7

8 24. A method of preparing an injectable depot gel composition comprising:

9 A) mixing a biocompatible polymer and a solvent whereby the solvent
10 dissolves the polymer and forms a viscous gel;

11 B) dispersing or dissolving a beneficial agent in the viscous gel to form a
12 beneficial agent containing viscous gel; and

13 C) mixing an emulsifying agent with the beneficial agent containing viscous
14 gel, said emulsifying agent forming a dispersed droplet phase in the beneficial agent
15 containing viscous gel to provide the injectable depot gel composition.

16

17 25. A method of preparing an injectable depot gel composition comprising:

18 A) mixing a biocompatible polymer and a solvent whereby the solvent
19 dissolves the polymer to form a viscous gel;

20 B) dispersing or dissolving a beneficial agent in an emulsifying agent to
21 form a beneficial agent containing emulsifying agent; and

1 C) mixing the beneficial agent containing emulsifying agent with the viscous
2 gel, said beneficial agent containing emulsifying agent forming a dispersed droplet
3 phase in the viscous gel to provide the injectable depot composition.
4

5 26. An injectable depot gel composition comprising:

6 A) a biocompatible polymer;
7 B) a solvent that dissolves the polymer and forms a viscous gel; and
8 C) an emulsifying agent in the form of a dispersed droplet phase in the
9 viscous gel.
10

11 27. A kit adapted to provide an injectable depot composition comprising as
12 kit components: (a) a biocompatible polymer and a solvent that dissolves the
13 polymer and forms a viscous gel; (b) emulsifying agent; and (c) beneficial agent.

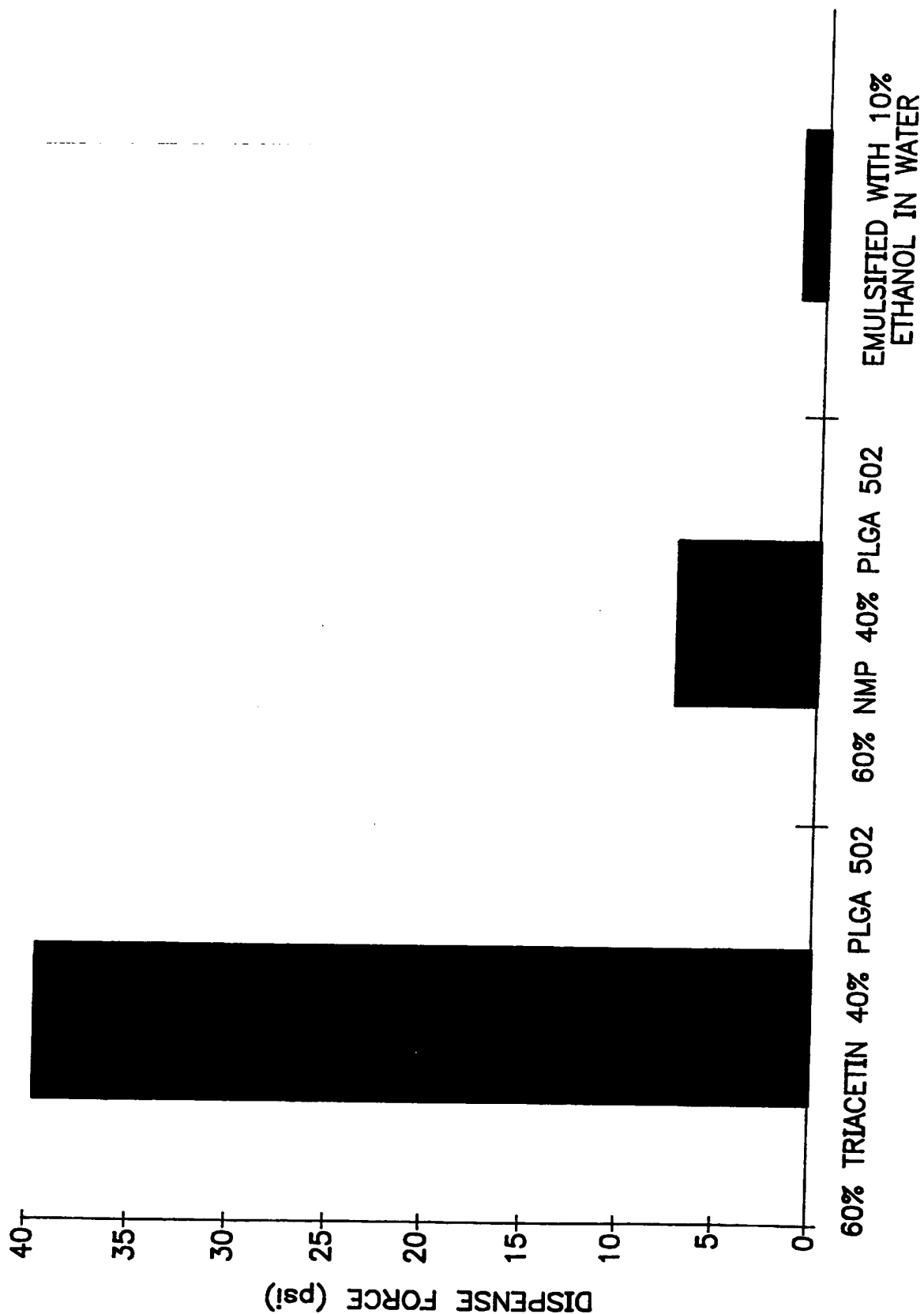


FIG. 1

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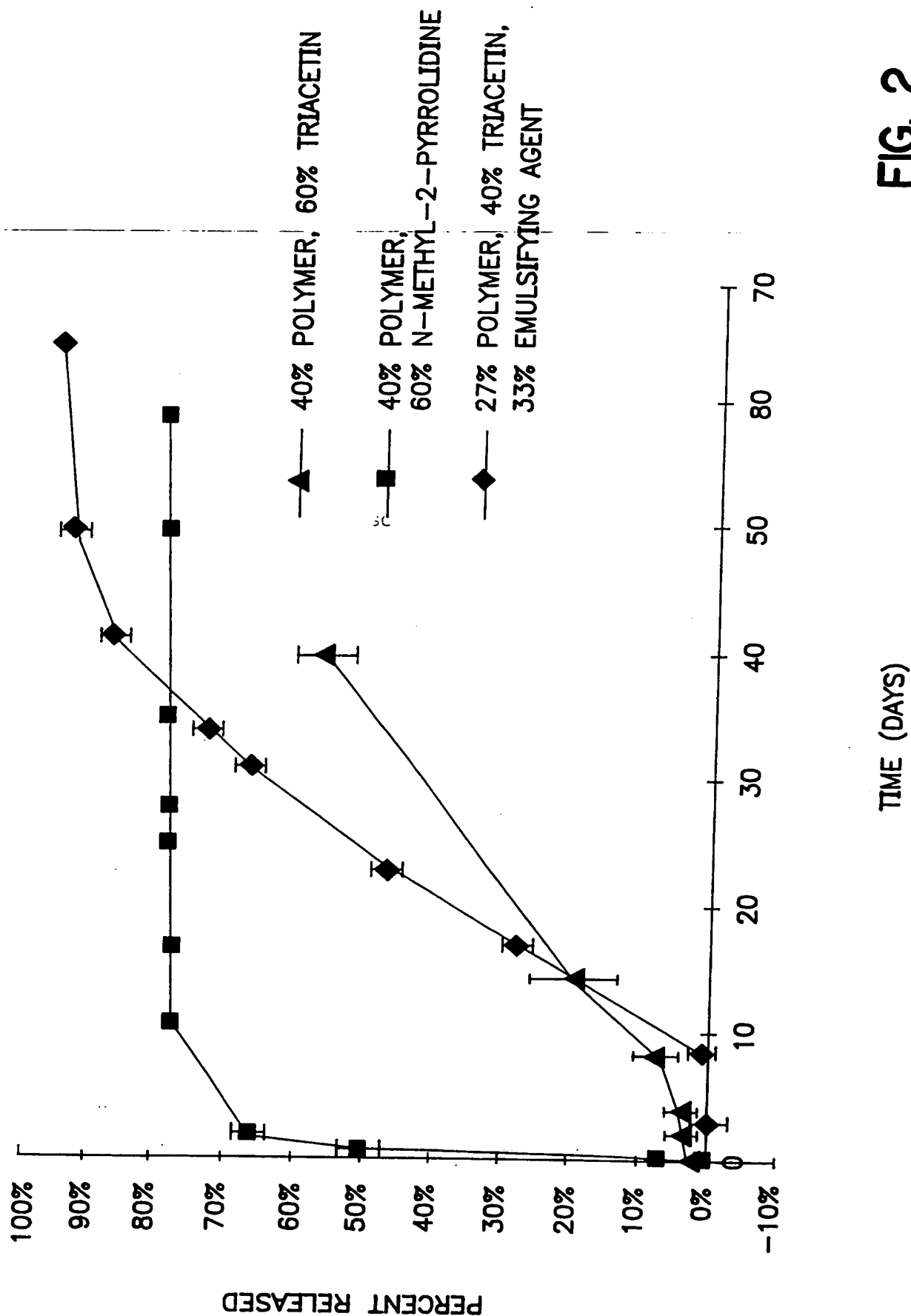


FIG. 2

3 / 3

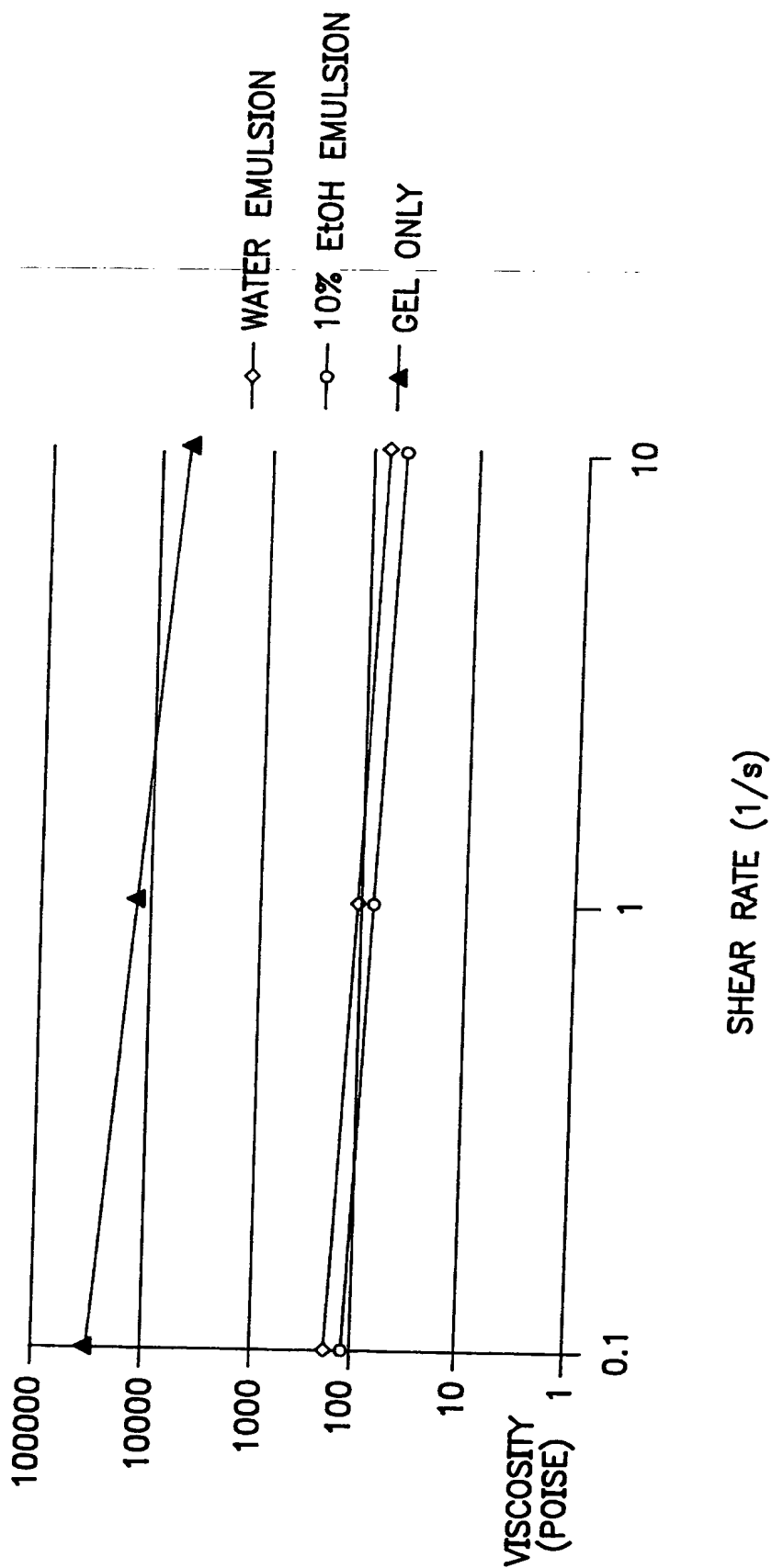


FIG. 3

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/34	A3	(11) International Publication Number: WO 98/27962 (43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23341 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		Published <i>With international search report.</i> (88) Date of publication of the international search report: 1 October 1998 (01.10.98)
(54) Title: INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF PREPARING THE COMPOSITION		
(57) Abstract		
<p>An injectable depot gel composition containing a polymer, a solvent that can dissolve the polymer and thereby form a viscous gel, a beneficial agent; and an emulsifying agent in the form of a dispersed droplet phase in the viscous gel. The injectable depot gel composition can be prepared by mixing the polymer and the solvent so that the solvent dissolves the polymer and forms a viscous gel. The beneficial agent is dissolved or dispersed in the viscous gel and the emulsifying agent is mixed with the beneficial agent containing viscous gel. The emulsifying agent forms a dispersed droplet phase in the viscous gel to provide the injectable depot gel composition. The injectable depot gel composition can deliver a beneficial agent to a human or animal with a desired release profile.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23341

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/34

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 27481 A (ATRIX LABORATORIES INC., U.S.A.) 19 October 1995 see claims 1-3, 7, 10-15, 19-27, 30 see page 4, line 26 - line 30 see page 14, line 3 - line 5 see page 14, line 22 - page 15, line 1 see page 18, line 33 - page 19, line 10 see page 26, line 21 - line 25 see page 30, line 12 - line 16 ---	1-3, 6, 7, 12-15, 17-21, 24, 26
X	WO 90 03768 A (SOUTHERN RESEARCH INSTITUTE, U.S.A.) 19 April 1990 cited in the application see claims 1-10, 27-37, 45 ---	1-3, 6, 7, 12, 19-22, 24-26

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17 July 1998

Date of mailing of the international search report

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PCT/US 97/23341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 242 910 A (N.C.DAMANJ) 7 September 1993 cited in the application see claims see column 5, line 20 - column 27 see column 5, line 64 - line 67 see examples IV,V,VI	1-3,6,8, 12,19, 24,26
X	EP 0 539 751 A (ATRIX LABORATORIES INC.,U.S.A.) 5 May 1993 cited in the application see claims	1-3,6,7, 12,13, 19-21, 24-26
X,P	WO 97 15287 A (MACROMED INC.,U.S.A.) 1 May 1997 see claims 1,5,8,13-17,34 see page 11, line 5 - line 21 see page 15, line 29 - page 16, line 9 see page 17, line 35 - line 37 see page 22, line 18 - line 24 see page 23, line 1 - line 12	1-3,6, 12-15, 19,22, 24,26
A	WO 91 05544 A (MEDINVENT,SE) 2 May 1991 see claims 1,2,10,12-14,18 see page 7, line 1 - line 3 see page 4, line 19 - line 31	1-3,6, 12-15, 17,24,26
A	US 5 318 780 A (T.X.VIEGAS ET AL.) 7 June 1994 see claims	1,2,6, 12,24,26
A	EP 0 640 647 A (COLAGEN CORPORATION,U.S.A.) 1 March 1995 see claims 1,3,5,44,47 see page 3, line 39 - line 41 see page 3, line 50 - line 52 see page 24, line 2 - line 5 see page 24, line 30 - line 34	1,2,6, 12-15, 24,26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/23341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9527481 A	19-10-1995	AU 684931 B AU 2129495 A BR 9507313 A CA 2187353 A EP 0754032 A JP 9511741 T US 5759563 A US 5744153 A	08-01-1998 30-10-1995 07-10-1997 19-10-1995 22-01-1997 25-11-1997 02-06-1998 28-04-1998
WO 9003768 A	19-04-1990	US 4938763 A AT 151257 T AU 4501789 A AU 5067793 A DE 68927956 D DE 68927956 T DK 57291 A EP 0436667 A EP 0773034 A IL 91850 A IL 107393 A JP 4503163 T US 5739176 A US 5725491 A US 5632727 A US 5278201 A US 5733950 A US 5340849 A US 5278202 A	03-07-1990 15-04-1997 01-05-1990 17-02-1994 15-05-1997 17-07-1997 03-06-1991 17-07-1991 14-05-1997 30-03-1995 29-06-1995 11-06-1992 14-04-1998 10-03-1998 27-05-1997 11-01-1994 31-03-1998 23-08-1994 11-01-1994
US 5242910 A	07-09-1993	AT 151282 T DE 69309701 D DE 69309701 T EP 0664696 A ES 2099977 T JP 8502289 T WO 9408562 A	15-04-1997 15-05-1997 30-10-1997 02-08-1995 01-06-1997 12-03-1996 28-04-1994
EP 539751 A	05-05-1993	US 5324519 A AT 163261 T AU 666676 B	28-06-1994 15-03-1998 22-02-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. J. Application No

PCT/US 97/23341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 539751 A		AU 2605492 A	29-04-1993
		CA 2079831 A	29-04-1993
		DE 69224456 D	26-03-1998
		DE 69224456 T	10-06-1998
		ES 2114901 T	16-06-1998
		JP 5305135 A	19-11-1993
		NZ 244581 A	25-06-1996
		US 5487897 A	30-01-1996
		US 5599552 A	04-02-1997
		US 5660849 A	26-08-1997
WO 9715287 A	01-05-1997	US 5702717 A	30-12-1997
		AU 7520096 A	15-05-1997
WO 9105544 A	02-05-1991	SE 465950 B	25-11-1991
		AT 143257 T	15-10-1996
		AU 632634 B	07-01-1993
		AU 6623790 A	16-05-1991
		CA 2067228 A	24-04-1991
		DE 69028710 D	31-10-1996
		EP 0497846 A	12-08-1992
		JP 5503921 T	24-06-1993
		SE 8903503 A	24-04-1991
		US 5614221 A	25-03-1997
US 5318780 A	07-06-1994	US 5587175 A	24-12-1996
EP 640647 A	01-03-1995	CA 2130295 A	27-02-1995
		JP 7196704 A	01-08-1995

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